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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
YASUHIDE TACHI et al)
Serial No. 024,111)
Filed: March 26, 1979)
For: NOVEL HYDROCORTISONE DERIVATIVE)

Examiner: Roberts
Art Unit: 125

DECLARATION

Hon. Commissioner of Patents and Trademarks
Washington, D.C.

Sir,

I, YASUHIDE TACHI, hereby declare the following:

1. I am a citizen of Japan residing at 1-22-3, Senkawa-cho, Toshimaku, Tokyo, Japan. I received Doctrate of Pharmacy from Tokyo College of Pharmacy in March 1978 and have been employed by TAISHO PHARMACEUTICAL CO., LTD. since April, 1966.

2. I am a member of the co-inventors of the captioned application.

3. Lack of any correlation between solubility and therapeutical effectiveness is apparent from the date of Table 1 of the present specification. For example, even if the diester is more soluble in vegetable oils or liquid carriers than the monoester as stated by Ercoli et al, therapeutical effectiveness

of the hydrocortisone monoester and diesters having 17-butyrate listed in Table 1 of the specification is as follows:

the 17-monobutyrate	1.70
the 17-butyrate 21-acetate	1.83
the 17-butyrate 21-propionate [compound (I)]	2.47
the 17,21-dibutyrate	1.57

Namely, therapeutical effectiveness of the 17-monobutyrate is lower than that of the 17-butyrate 21-acetate and the 17-butyrate 21-propionate, but higher than that of the 17,21-dibutyrate. In view of the above, the increase of the solubility stated by Ercoli et al does not relate to that of therapeutical effectiveness.

4. The increase rate of the average score described in Table 1 of the present specification does not mean the increase rate of therapeutical effectiveness. In the vasoconstrictor test of the present specification, the claimed compound, i.e., the compound (I), obtains 2.47 points out of possible 3 points. Accordingly, a 28 % increase in the average score described at page 4 of the response filed November 2, 1979 is a highly significant advance, since there is little difference of about 55 % between the point(1.93) of hydrocortisone 17-valerate 21-acetate and the maximum point(3.0). A 28 % increase in the average score does not mean a 28 % increase in effectiveness. In order to establish such an

increase for superiority by another method, shown in Table A are the results of the vasoconstrictor test which were obtained by following the same procedure described at page 4 of the present specification and using petrolatum-based ointments containing 0.1×2^{-2} % and 0.1×2^{-4} % of the compound (I) as the test compounds.

TABLE A.

AVERAGE SCORE IN VASOCONSTRICTOR TEST

Compound	0.1×2^{-2} %	0.1×2^{-4} %
Compound (I)	2.26	1.83

These results mean that the compound (I) diluted to 0.025 % and about 0.006 % shows 2.26 and 1.83 in the average score, respectively. From the results, the concentration at which the compound (I) shows 1.93 in the average score is estimated at about 0.01 %. From Table 1 of the present specification and the above, the effectiveness of the compound (I) of which concentration is about 0.01 % equals to that of hydrocortisone 17-valerate 21-acetate of which concentration is 0.1 %. In other words, the compound (I) is about 10 times hydrocortisone 17-valerate 21-acetate in therapeutical effectiveness. Therefore, a 28 % increase in the average score described above means about a 1000 % increase in effectiveness.

I believe that such an increase is unexpected superiority in the art of anti-inflammatory agents.

5. I further state that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Yasuhide Tachi

YASUHIDE TACHI

Date: May 28, 1980